Remarks

Claims 115-120, 133, 136 and 139 are cancelled.

Claims 34, 43, 56, 88-91, 93, 96-99, 101-103, 108-111, 113, 114, 121, 124, 127, 130-132, 134, 135, 137 and 138 are amended. Support for the amendments can be found, for example, on page 34, lines 1-2 and 25-26; page 50, line 22; page 51, lines 19-23; and page 52, line 12 of the specification.

Claims 140-148 have been added. Support for the new claims can be found throughout the specification and, for example, on page 5, line 14 through page 7, line 2.

Claims 89, 97, 109, 132, 135 and 138 are withdrawn as being drawn to a non-elected species. Applicant requests consideration of the withdrawn claims in the event a generic claim is allowed.

No new matter has been added.

Claims 34, 43, 56, 88-91, 93, 96-99, 101-105, 108-111, 113, 114, 121-132, 134, 135, 137, 138 and 140-148 are pending.

Objection to the Information Disclosure Statement

The Examiner has indicated that the Salomone et al. reference (C19 of PTO Form 1149 submitted June 11, 2003) has not been considered because the date of the reference was missing on the form. A new PTO Form 1449 is submitted herewith, which indicates November 2000 as the month and year of publication of this reference. Applicant requests that the Examiner consider the reference in view of this submission.

Interview with Examiners Ruixiang Li and Yvonne Eyler

Applicant would like to thank Examiners Li and Eyler for granting an interview with Applicant's representatives. During the interview the enablement rejection regarding the use of any agent to downregulate any EDG receptor signaling in any artery for increasing vasodilation or inhibiting vasoconstriction was discussed. Additionally, the written description rejection of the term "neuroprotective agent" was also discussed briefly. Potential claim amendments were discussed. Although specific agreement regarding the claims was not reached, Applicant wishes to thank the Examiners for agreeing to reconsider the arguments presented in the previous response.

Rejection of Claims Under 35 U.S.C. §112, first paragraph

Claims 34, 43, 56, 88-91, 93, 96-99, 101-105, 108-111, 113, 114, 121-131, 134 and 137 are rejected under 35 U.S.C. §112, first paragraph, as not being sufficiently enabled so that one skilled in the art can use the invention commensurate in scope with these claims.

Receptors:

The Examiner maintains that the specification does not provide teachings of the involvement of receptors other than EDG-3 in vasoconstriction. Applicant respectfully disagrees.

Applicant's disclosure suggests the involvement of all S1P-binding EDG receptors in S1P-induced vasoconstriction (e.g., EDG-1, EDG-3, EDG-5 and EDG-8). Applicant's data clearly demonstrates EDG-3 involvement but it does not preclude involvement of other EDG receptors in S1P-induced vasoconstriction.

The Examiner maintains that the specification teaches against the involvement of EDG-5 signaling in S1P-induced vasoconstriction. The teachings referred to by the Examiner do not negate involvement of EDG-5 in vasoconstriction. First, the Examiner states that the antisense experiment demonstrates that EDG-5 is not involved in S1P-induced vasoconstriction. Applicant, however, maintains that the antisense experiment says nothing of EDG-5 involvement in vasoconstriction. It is known to ordinary artisans in the antisense field that a negative antisense result is not to be regarded as a conclusive result as there are many variables that can affect the outcome of an antisense experiment (e.g., turnover rate of the EDG-5 receptor). Accordingly, one of ordinary skill in the art could not conclude from Applicant's experiment that EDG-5 is not involved in S1P-induced vasoconstriction. Second, the Examiner maintains that Applicant's teaching that suramin antagonizes only the EDG-3 receptor is also a negative teaching of EDG-5 receptor involvement in S1P-induced vasoconstriction. Applicant again respectfully disagrees. This finding merely indicates that some agents have receptor specificity. In this case, Applicant is providing an example of an agent that functions through EDG-3 receptor. It says nothing of EDG-5 and, therefore, cannot be construed as teaching against EDG-5 involvement in S1P-induced vasoconstriction.

Additionally, as stated previously, others have now also shown that EDG-5 is involved in vasoconstriction induced by S1P, confirming Applicant's teachings. Ohmori et al., 2003, for instance, found that an antagonist to S1P(2) (i.e., EDG-5) inhibited vasoconstriction in cardiac

smooth muscle cells. Applicant emphasizes that the post-filing reference is relied upon to demonstrate that the instant specification was enabling at the time of filing.

Applicant maintains that the specification supports the involvement of EDG receptors in addition to EDG-3 in mediating vasoconstriction. However, in an earnest effort to expedite prosecution, Applicant has amended the claims to read on EDG-3 and EDG-5 receptor signaling only.

Agents:

The Examiner states that the specification does not teach how to make the broad genus of agents. The Examiner maintains that the specification's disclosure of two EDG receptor inhibitors, sphingosine and suramin, is insufficient. Applicant respectfully disagrees.

The standard for enablement is whether undue experimentation would be required for one of ordinary skill in the art to practice the claimed invention. An analysis of the factors set forth in In re Wands provides a determination of whether experimentation is undue. In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicant asserts that based on an analysis of these factors, discussed below, experimentation is not undue.

Based on the guidance provided by the specification, one of ordinary skill is able to make, screen and use further EDG receptor inhibitors. The specification defines EDG receptor inhibitors as agents that decrease the level of EDG receptors at either the mRNA or protein level, agents that interfere with EDG receptor signaling (e.g., by preventing EDG receptor binding to an agonist such as a naturally occurring ligand, or interfering with a downstream factor required for EDG receptor signal transduction). (See, for example, page 20, lines 21-29; page 22, lines 3-7 and lines 20-33; and page 23, lines 1-21.) The application provides examples of EDG receptor inhibitors, such as sphingosine and suramin, among others. (See, for example, Rho pathway inhibitors HA1077 and Y27632 described on page 23, lines 13-15.) The specification teaches methods for making further agents to be used in the claimed methods (pages 38, line 11 – page 39, line 29). The specification also identifies PCT published applications WO 99/35259 and WO 99/46277 as teaching methods for making and identifying EDG receptor antagonists (page 43, lines 20-22). The specification also provides methods for screening agents to be used in the claimed methods (page 39, line 30 – page 42, line 26 for binding assays; and page 42, line 27 – page 43, line 19 for vasoconstriction assays). Furthermore, the specification teaches how to use the agents in the claimed methods, including subjects to be treated, effective amounts to be

administered, formulations, agents to be administered alongside EDG receptor inhibitors, routes of administration, and the like (see pages 23-38).

The level of skill in the art has an important effect on the amount of guidance which must be provided to enable the invention. The court in In re Howarth stated that "[i]n exchange for the patent, [the applicant] must enable others to practice his invention. An inventor need not, however, explain every detail since he is speaking to those skilled in the art." In re Howarth, 654 F.2d 103, 105 (C.C.P.A. 1981). For the standard procedures contemplated in the application, the level of skill in the art is high. In the Wands case, for example, the court's decision turned on the "high level of skill in the art at the time the application was filed", and that "all of the methods needed to practice the invention were known." Wands at 740, 8 U.S.P.Q.2d at 1406. Applicant maintains that the same conclusions with respect to the state of the art and the level of skill in the art are true in the instant case, and therefore must weigh heavily in favor of a finding that undue experimentation is not required. Furthermore, the specification provides evidence that identifying EDG receptor inhibitors can be accomplished using only routine methods. Applicant's specification recites PCT applications WO 99/35259 and WO 99/46277 (page 43, lines 20 and 21), which describe methods for identifying EDG receptor antagonists, demonstrating that the synthesis and screening of these compounds is known in the art.

Finally, although working examples are not required if the invention is otherwise disclosed in a manner such that one of skill in the art would be able to practice the invention without undue experimentation, examples of agents are provided by the Applicant as documented above.

Therefore, one of ordinary skill in the art is able to make, identify, test and use agents in the claimed methods based on the teaching in the specification and the state of the art at the time of filing.

Arteries:

The Examiner maintains that the specification does not enable the increased vasodilation or inhibited vasoconstriction through the downregulation of EDG receptor signaling in any arteries other than cerebral arteries.

Applicant respectfully traverses the Examiner's rejection. The specification teaches, inter alia, that sphingosine-1-phosphate (S1P) induces vasoconstriction in cerebral and coronary arteries. The specification provides data that show the contractile response in coronary arteries

to S1P (see for example Table 1; almost 20% of the contractile response to KCl). The specification further teaches that EDG-1, -3, -5 and -8 receptor subtypes (which all have S1P as an agonist) are expressed in cerebral, coronary and other peripheral arteries. In addition, Applicant herewith provides additional data, as Supplemental Figure 1, which also show the vasoconstrictive effects of S1P on coronary arteries in rats (measured as the percentage of KCl constriction). The vasoconstriction is shown to increase with increasing S1P concentration. If the Examiner desires, Applicant can submit Supplementary Figure 1 in a Declaration.

Applicant provided in the instant specification an explanation for why a vasoconstrictive effect might be weaker or not observed in peripheral arteries. Applicant determined that the level of S1P phosphatase was increased in arteries with little or no vasoconstrictive response to S1P and explained that an increase in this enzyme would reduce the amount of S1P available for receptor binding (see page 51, lines 14-23). S1P phosphatase converts S1P to sphingosine, an agent specifically taught by the Applicant to be an inhibitor of EDG receptor signaling induced vasoconstriction. These teachings do not preclude the involvement of EDG receptor signaling in vasoconstriction of the peripheral arteries. Rather, the teachings suggest that the vasoconstrictive effects of S1P are masked by the action of S1P phosphatase on S1P. Under conditions in which levels of S1P-phosphatase are reduced, vasoconstriction would be observed.

Furthermore, as stated previously, the vasoconstrictive effects of S1P in arteries other than cerebral arteries have been confirmed by others. The references cited herein have been provided to the Examiner for his review previously. Applicant does not rely on these references to enable the pending claims. Rather, these references demonstrate that the specification was enabling at the time of filing. Ohmori, et al. confirm that S1P induces vasoconstriction in human coronary artery smooth muscle cells (see Ohmori, T., et al., Cardiovasc Res 2003 Apr; 58(1):170-7). Bischoff et al. confirm that S1P is able to induce constriction of renal and mesenteric vessels *in vitro* and reduce blood flow in the same *in vivo* (see Bischoff, A., et al., 2000. Br. J. Pharmacol. 130, 1871-1877; Bischoff, A., et al., 2000. Br. J. Pharmacol. 130, 1878-1883).

Applicant therefore maintains that methods for increasing vasodilation or inhibiting vasoconstriction in peripheral arteries were enabled by the specification at the time of filing. However, in an earnest effort to expedite prosecution, Applicants have amended the claims to read on cerebral arteries alone or cerebral and coronary arteries.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims 34, 43, 56, 88-91, 93, 96-99, 101-105, 108-111, 113, 114, 121-131, 134 and 137 under 35 U.S.C. §112, first paragraph.

Rejection of Claims Under 35 U.S.C. §112, first paragraph

The Examiner has maintained the rejection of claim 104 under 35 U.S.C. §112, first paragraph. The Examiner argues that the claim does not require the term "neuroprotective agent" to possess any specific activity, structure or other distinguishing feature. The Examiner states that the claim is so broad as to encompass any agent that protects the nervous system as well as agents that are to be discovered in the future.

Applicant respectfully traverses the Examiner's rejection. The term clearly indicates that agents falling within the category of neuroprotective agent have a specific activity. As demonstrated by the Examiner himself, a neuroprotective agent is an agent that protects the nervous system.

The Examiner states that no representative species were disclosed in the specification. Applicant maintains that since this term represents an art-recognized category, such examples are not required. One of ordinary skill in the art would be aware of such species. In Applicant's previous response, Applicant indicated that this term was used in over 21,000 articles available through the PubMed online database, demonstrating that the term is art-recognized. Furthermore, the term is also recited in the claims of a number of issued U.S. patents. In particular, in U.S. Patent 5,916,910 filed on June 4, 1997 (prior to the priority date of the instant application), the term is recited in the claims and a long list of such agents is provided.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claim 104 under 35 USC §112, first paragraph.

Rejection of Claims Under 35 U.S.C. §112, second paragraph

The Examiner maintains the rejection of claim 104 under 35 U.S.C. §112, second paragraph for failing to "particularly point out and distinctly claim the subject matter which applicants regard as the invention."

The Examiner rejects claim 104 based on the recitation of the term "neuroprotective agent". According to the Examiner, the term is indefinite. Applicant respectfully disagrees with

the Examiner's conclusion for the reasons stated herein as well as those asserted in the response to the previous Office Action.

It is clear that the "neuroprotective agent" is an art recognized term as evidenced by its usage in both the literature and patent database. (See Rejection under 35 U.S.C. § 112, first paragraph, above.) Additionally, Applicant maintains that the ability of the Examiner to ascribe a definition to the term speaks to the unambiguousness nature of the term. The term is definite.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claim 104 under 35 U.S.C. § 112, second paragraph.

Objection of Claims

The Examiner has objected to claims 89, 97, 104, 109, 115-120, 132, 133, 135, 136, 138, and 139 for reciting unelected species. As currently amended, claims 89, 97, 109, 132, 135 and 138 recite the unelected EDG-5 receptor signaling or its inhibitors, and claim 104 recites unelected second agents. Claims 115-120, 133, 136 and 139 have been cancelled. Claims 89, 97, 109, 132, 135 and 138 have been withdrawn as being drawn to unelected species.

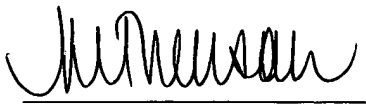
The Examiner is respectfully reminded that Applicant is not required to cancel the unelected subject matter as the subject matter pertains to a species election. Therefore, the non-elected species present in claims 89, 97, 109, 132, 135 and 138 and claim 104 are withdrawn from consideration and are not currently being examined. However, these claims need not be deleted or amended. 37 C.F.R. §1.141 states that "upon the allowance of a generic claim, applicant will be entitled to consideration of the claims to additional species which are written in dependent form or otherwise include all of the limitations of an allowed generic claim". Accordingly, since these species elections were made for examination purposes only, Applicant is not obligated to amend claim 104 nor to cancel claims 89, 97, 109, 132, 135 and 138.

Applicants respectfully request that the Examiner reconsider and withdraw this objection to claims 89, 97, 104, 109, 115-120, 132, 133, 135, 136, 138, and 139.

Summary

It is believed that all of the pending claims are in condition for allowance. If the Examiner has any questions or comments, he is encouraged to contact Applicant's representative at the number listed below.

Respectfully Submitted,



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